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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/486,613	02/29/2000	DEBORAH C. MASH	N08-002	8931

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EXAMINER	
JIANG, SHAOJIA ANNA	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/486,613	MASH, DEBORAH C.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on October 25, 2004 wherein claim 30 has been amended. Currently, claims 1-2, 4-9, and 25-30 are pending in this application.

It is noted that claims 3, 10-24 are cancelled previously.

Claims 1-2, 4-9, and 25-30 are currently under examination on the merits.

As indicated in the previous Office Action July 16, 2002, this application is a 371 of PCT/US98/18284 which claims priority to provisional application Serial No. 60/057,921.

Applicant's remarks filed October 25, 2004 with respect to the objection of claims 27-28 and 29-30 made under 37 CFR 1.75 as being a duplicate of claims of record stated in the Office Action dated April 30, 2004 have been fully considered and are found persuasive. Therefore, this objection is withdrawn.

Applicant's remarks filed October 25, 2004 with respect to the rejection of claims 1-2, 4-5, and 25-30 made under 35 U.S.C. 112 first paragraph for containing new subject matter ("a patient to alleviate pain without addition") of record stated in the Office Action dated April 30, 2004 have been fully considered and found persuasive to remove the rejection since the specification is seen to provide support for this limitation. Therefore, the said rejection is withdrawn.

Applicant's remarks filed October 25, 2004 with respect to the rejection made under 35 U.S.C. 103(a) as being unpatentable over under 35 U.S.C. 103(a) as being unpatentable over Epstein et al. (3,715,361) and GB 841,697 in view of Bagal et al. and Hussain (4,464,378) and Applicant's admission regarding the prior art in the specification (see page 1-3) of record stated in the Office Action dated April 30, 2004 have been considered and found persuasive to remove this particular rejection as to claims 1-5 and 25-30, since the cited prior art is seen to fail teach or suggest that ibogaine or its known metabolite, noribogaine, alone or in absence of an opioid analgesic, is useful in a method of treating or alleviating pain in a patient.

Moreover, Compound I, II, III, IV, of Epstein et al. (3,715,361) having analgetic activity are not ibogaine or noribogaine; nor are they structurally similar to ibogaine or noribogaine, since they have R and R' substituents as –CHO or $COCH_3$ whereas ibogaine or noribogaine have none of R and R' substituents. Thus, the compounds of Epstein et al. are not seen to render ibogaine or noribogaine obvious.

Therefore, the said rejection as to claims 1-5 and 25-30 is withdrawn.

The following is the new ground(s) of rejection(s).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 9 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular and specific opioid antagonists, in co-administering noribogaine employed in the claimed method, does not reasonably provide enablement for any substances or compounds represented by "opioid antagonists".

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of treating a patient to alleviate pain comprising administering noribogaine and one or more opioid antagonists.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims may reasonably encompass not only those known but also unknown opioid antagonists as of the instant filing date, even those future known opioid antagonists.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "opioid antagonists", recited in the instant claims is purely functional distinction. Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during

the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)). The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co*. Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) the ***combination*** of any compounds represented by "opioid antagonists" and noribogaine.

See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in

particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added). In the instant case, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having claimed functional properties in the pharmaceutical compositions herein to be administered to a host. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

Further, these recitations may broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date, as discussed above. These recitations broadly encompass those known and **unknown** compounds having the recited functions as of the instant filing date. Note those **future known** compounds yet to be discovered and/or made. Hence, those unknown or future known compounds encompassed by claim 1 herein must require to additional or future research to discover, establish or verify their usefulness. Therefore, as indicated in the previous Office Action, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

The presence or absence of working examples and the quantity of experimentation necessary:

Moreover, it is noted that the specification fails to provide working examples, i.e., testing results or data to demonstrate the instant combination of "opioid antagonists" and noribogaine to be administered to a host, in treating pain.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any "opioid antagonists" in the instant claims. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the embodiments of any known and unknown compounds having the function encompassed in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all combinations encompassed in the instant claims in the claimed compositions to be administered to a host, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 and 25-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Olney (US 5925634, PTO-892).

Olney discloses that ibogaine alone or in absence of an opioid analgesic is useful in treating neuropathic pain wherein ibogaine is the sole agent for alleviating pain. See the title, abstract, col.7 lines 16-18; claim 1. Olney also discloses the range of the dose about 1-50 mg/kg per day or about 5-100 mg/kg/day which touch or overlap with the claimed range herein (see col.15 lines 35-38), and various administration routes, e.g., orally (see col.14-15).

Given the fact that noribogaine is a known metabolite of ibogaine (noribogaine is known to be 10-Hydroxyibogamine, a de-methyl-ibogaine; ibogaine is 10-methoxyibogamine), as Applicant admits and acknowledges regarding the prior art in the specification (see page 3), noribogaine was necessarily produced in the patient's body upon ingestion of ibogaine by hydrolysis in the body. Note that the court ruled that the metabolite of loratadine called descarboethoxyloratadine or "DCL" was INHERENTLY anticipated by loratadine (Claritin ™) because it was necessarily produced in the patient's body upon ingestion of Claritin ™. See Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003).

Further, Olney discloses that ibogaine can be used in combination with additional drugs (see col.7 line 27-32) which are not opioid analgesic agents.

Thus, Olney's method anticipates the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olney (US 5925634) or GB 841,697 (of record) in view of Hussain (4,464,378) and Applicant's admission regarding the prior art in the specification (see page 1-3).

The same disclosure of Olney has been discussed in the 102(e) rejection set forth above.

GB 841,697 discloses that ibogaine is an analgesic agent, and is therefore useful in an analgesic composition for treating or alleviating pain. The effective amount or dose of ibogaine, 20-40 mg, is also taught in GB 841,697. See abstract, col.1-2, and claims 1-5.

The prior art does not expressly disclose the employment of noribogaine in combination with an opioid antagonist such as naloxone, naltrexone and nalorphine in a method of treating a patient to alleviate pain. The prior art does also not expressly

disclose the particular effective amounts of naloxone, naltrexone and nalorphine to be administered with noribogaine in the claimed method.

Hussain teaches that opioid antagonists such as naloxone, naltrexone and nalorphine are well known analgesics and therefore useful in a method of treating or alleviating pain in a patient. See col.1 lines 44 and 56-57, col.3 lines 24-27, and claims 1-2.

Applicant's admission regarding the prior art in the specification (see page 3) teaches that noribogaine is a known metabolite of ibogaine and opioid antagonists such as naloxone, naltrexone and nalorphine are known analgesics and useful in a method of treating or alleviating pain in a patient.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ noribogaine in combination with an opioid antagonist such as naloxone, naltrexone and nalorphine in a method of treating a patient to alleviate pain, and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ noribogaine in combination with an opioid antagonist such as naloxone, naltrexone and nalorphine in a method of treating a patient to alleviate pain since opioid antagonists such as naloxone, naltrexone and nalorphine are well known to be useful in a method of treating a patient to alleviate pain.

Therefore, one of ordinary skill in the art would have reasonably expected that combining noribogaine and an opioid antagonist herein known useful for the same

purpose (i.e., treating a patient to alleviate pain) in a composition to be administered would improve the therapeutic effect for alleviating pain.

Moreover, the combination of ibogaine and additional drugs taught by Olney is seen to provide the motivation for the combination claimed herein.

Additionally, one of ordinary skill in the art would have been motivated to optimize the effective amounts of active ingredients in the composition because the effective amounts of noribogaine and an opioid antagonist herein are known in the art. In addition, the optimization of amounts of active agents to be administered is considered well within the skill of artisan.

Since all active composition components herein are known to useful to treat a patient to alleviate pain, it is considered prima facie obvious to combine them into a single composition to form a third composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Applicant's arguments filed on October 25, 2004 with respect to the rejection made under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection above.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner, AU 1617
January 4, 2005